Comment


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Abstract: Recently, some drugs were approved to control Monkeypox (MPX), among them tecovirimat. This was recently approved by regulatory agencies around the world, the paper of Zovi et al. entitled Pharmacological Agents with Antiviral Activity against Monkeypox Infection highlight it as safe and effective, although the safety data are still not very robust. In this Comment, we present some theoretical evaluations of its safety, considering that for use in humans it is essential to have a rich scientific literature in the area. After a series of analyses, a potential risk of liver, respiratory and kidney damage was found in addition to carcinogenic potential. Thus, while we agree that there is a need for rapid responses to infection, we reinforce that well-designed and adequately powered studies should not only focus on investigating the pharmacological efficacy of tecovirimat but also demonstrate its safety in humans. Therefore, in this Comment, we present some concerns that may help in formulating a safer treatment for patients infected with Monkeypox virus (MPXV).

Keywords: Monkeypox; tecovirimat; physicochemical descriptors; pharmacokinetic; toxicity; ADME-T

Recently, Zovi et al. 2022 [1] suggest in the paper titled “Pharmacological Agents with Antiviral Activity against Monkeypox Infection” that although the epidemic caused by Monkeypox virus (MPXV) is milder than COVID-19 there is a need to ensure that epidemiological and control measures are widely available to limit the spread of the disease. Among the different drugs discussed by the authors, tecovirimat stands out for having a higher survival rate than placebo, with few adverse effects. However, this information was obtained from few studies, and this lack of information requires further research to ensure the robustness of the data.

Additionally, although the infection by the circulating variant in the current epidemic of Monkeypox (MPX) appears to be mild and self-limited [2], the possibility of initiating a treatment without a robust safety analysis in risk groups, mainly composed of children and immunosuppressed patients, is worrying. Thus, a broader analysis of potential adverse effects based on toxicological analysis would provide greater safety for treatment with tecovirimat.

Tecovirimat, also known as TPOXX, is a small-molecule-based antiviral agent that exerts its antiviral activity against orthopoxviruses, including Monkeypox virus (MPXV). The drug acts as an inhibitor of the envelope protein VP37, which is critical for the production of extracellular virus. By interfering with the cellular transmission of the virus, TPOXX effectively prevents disease onset [3,4]. Although preclinical and clinical studies have demonstrated the efficacy of tecovirimat in reducing disease severity and improving
clinical outcomes, the potential adverse and toxicological effects of this agent need to be carefully evaluated.

In this perspective, this Comment highlights some potential adverse effects of the TPOXX and thus complements the understanding of its toxicity, offering a complement to the work realized by the authors. From ChemBL [https://www.ebi.ac.uk/chembl/ (accessed on 16 March 2023)], T3DB [http://www.t3db.ca/ (accessed on 16 March 2023)], PubChem [https://pubchem.ncbi.nlm.nih.gov/ (accessed on 16 March 2023)], DrugBank [https://go.drugbank.com/ (accessed on 16 March 2023)], and ChemSpider [https://chemspider.com/ (accessed on 16 March 2023)], several structural, physicochemical, and toxicological parameters of TPOXX suggest chemical medical problems (Figure 1).

Figure 1. Physicochemical descriptors and toxicity-related properties of tecovirimat from ChemBL, T3DB, PubChem, DrugBank, and ChemSpider.

Chemically reactive compounds have the potential to alter off-target proteins, leading to adverse effects such as immunotoxicity and idiosyncratic hypersensitivity reactions [5]. In studying the physicochemical descriptors of a major pharmacological bank, Hughes et al. found that the combination of a high LogP and low TPSA (Topological Polar Surface Area) increased the likelihood of promiscuous drug binding. According to their studies, a drug must have a LogP value > 3 and a TPSA value < 75 to be 2.5 times more toxic than clean effects [5]. TPOXX has a LogP and a TPSA value of 3.818 and 74.490, respectively.

Drug-induced liver injury (DILI) has become the most common safety issue in the withdrawal of drugs from the market over the past 66 years [6]. Unfortunately, TPOXX can cause liver dysfunction, as shown by an analysis of two computational predictors of hepatotoxicity generated from a dataset containing the chemical structure of 951 compounds reported to have a wide range of effects on the liver in various mammalian species, including humans, rodents, and non-rodents [7].

It is also worth noting that renal excretion of unchanged compounds is one of the major pathways for drug elimination and plays an important role in pharmacokinetics. Values above 5.0 mL/min/kg are ideal, as they allow the drug to act in the body in a controlled manner over a longer period. Using an in silico prediction model for renal clearance (CLR) with a dataset of 401 drugs, TPOXX achieved a CLR = 1.89 mL/min/kg, which means that the drug remains in the body for approximately twice the maximum time recommended by the established parameter, which may lead to prolonged therapeutic and adverse effects [8]. It is generally accepted that among the various toxicological endpoints
of chemical substances, carcinogenicity is of great importance because of its serious effects on human health. Studies systematically investigating prescription drugs have successfully identified drugs associated with cancer risk \[9,10\]. In this context, TPOXX has a reasonable chance of being carcinogenic according to its theoretical TD\(_{50}\) value. In silico assays using the PreADMET tool also indicate a positive result for carcinogenesis in mice and rats with this compound. Moreover, according to the micronucleus assay \[11\], the molecule is also classified as genotoxic, which poses a significant risk for promoting cancer in the human organism.

_Tetrahymena pyriformis_ is the most commonly used protozoan for laboratory research, and its toxicity is often used as a toxic endpoint. An important predictive model for the toxicity of _T. pyriformis_, which includes an extensive dataset (1571 chemicals), shows that TPOXX has a high toxic potential for this microorganism, with a pIG\(_{50}\) of 0.4 log µg/L (optimal: <−0.5 log µg/L). Finally, it may cause respiratory toxicity in the body, especially in people with a pathological respiratory condition.

Therefore, although Zovi et al. 2022 \[1\] suggest that tecovirimat may be the best option for the treatment of MPX, its theoretical toxicity profile referenced in this Comment raises the possibility that this drug is not a safe treatment. In this sense, Fatima et al. 2022 \[3\] report that despite preliminary data indicating the promising efficacy and safety of this drug in the treatment of MPX, only a large-scale randomized control trial can provide a more robust conclusion. In this work they also question the drug’s safety, arguing that the received data come mainly from studies in animal models using related orthopoxviruses and that the safety in humans was evaluated by analyzing the adverse reactions only in healthy volunteers. Finally, they reinforce that animal studies can serve as an alternative; however, their results cannot be directly compared with clinical trials in humans.

Tecovirimat was recently approved as the first antiviral against smallpox, where it was generally well tolerated after a once-daily oral dose for 14 days in human volunteers \[12–14\]. When the U.S. Food and Drug Administration (FDA) considered approving the drug in 2018 to treat smallpox, the agency acknowledged that it would not be feasible or ethical to test the drug by infecting people with this virus or another orthopoxvirus.

It was not until the second half of 2022 that the therapeutic efficacy of this drug against MPXV was evaluated in a very limited number of patients and through work with low scientific rigor, usually uncontrolled cohort studies \[14–16\]. Therefore, despite the existence of four robust clinical trials in development (NCT05559099, NCT05534165, NCT05534984, NCT05597735), we stress that we cannot speak with certainty about the efficacy and safety of the drug. The limitations of published studies include small numbers of patients, the lack of a control group, and selection bias. Thus, further large-scale studies are needed to investigate antiviral efficacy, dosing, and adverse events.

Appropriately powered and well-designed clinical trials should not only focus on investigating the pharmacological efficacy of tecovirimat against MPXV infection but also demonstrate the safety of this drug in terms of adverse and toxicological effects. Finally, we agree that the epidemiological emergency often requires some steps to be accelerated in clinical drug research. However, in this Comment, we present some concerns that may help in formulating a safer treatment for patients infected with MPXV.

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